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INTERIM
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STUDIES OF NICOTINE ACTION UPON MEMORY CONSOLIDATION

The research project beyond establishing several of the interrelationships between the behavioral effects of nicotine and several of its biologically active metabolites and certain specific putative neurotransmitter molecules active in brain metabolism has, within the past year, specifically concerned itself with the interaction of these events and experimentally-induced retrograde amnesia. Whereas previous research has fundamentally established a strong basis for changes in brain serotonin metabolism associated with retrograde amnesic events, such as electroconvulsive shock (ECS), in mice and further that such ECS is temporally contiguous with an inhibition of cerebral protein synthesis sufficient to account for the amnesic phenomenon (Essman and Heldman, 1972), several experiments were systematically undertaken in order to further examine the direct role of cerebral serotonin in mediating the amnesic effect. In previous progress reports, as well as published papers, we have indicated that nicotine as well as several of its biologically active metabolites may well antagonize the amnesic effect of ECS by blocking the cerebral changes in serotonin metabolism usually attendant upon ECS treatment. Several experiments have further corroborated this result and supported the hypothesis that not only is the change in serotonin metabolism necessary to experimentally produce a retrograde amnesia, but an inhibition of protein synthesis is also such a requisite.

Both such changes haje been shown to be attenuated or blocked by nicotine.

Specific experiments have considered the age dependent nature of experimentally-induced ammesia and the extent to which such age dependency includes developmental as well as critical age phenomena dependent upon brain serotonin metabolism. Specifically, subcellular fractionation of the mouse cerebral cortex has revealed that such changes reside within the presynaptic nerve ending (synaptosome). Amnesic effects, as well as effects upon cerebral protein synthesis, appear to be specific to an initial increase in local concentration of serotonin, as supported by experiments within which this amine was micro-injected into the hippocampal region of the brain; retrograde ammesic effects as well as inhibition of protein synthesis was in evidence under such conditions and these effects appeared to be specific to serotonin, inasmuch as analogs thereof or other biogenic amines did not provide for either the amnesic or synthetic effects.

Whereas an age specific phenomenon for susceptibility to retrograde amnesia was previously shown for ECS-induced conditions, it was further shown that intracranial 5-HT treatment not only induced an age dependent ammesia but also a highly correlated age dependent inhibition of protein synthesis.

The indole amine changes in brain as a function of nicotine have been indicated such that a marked increase in brain 5-hydroxytryptamine (5-HT) turnover time results. This effect has been shown to be regionally specific in brain as well as time dependent following nicotine treatment. The changes in the relationship between 5-HT and its metabolite in brain 5-HIAA, has also been shown to be re-

gionally specific over time.

Investigation of cell specific populations isolated following in vivo treatment with nicotine indicated that increases in 5-HT content were specific to both neurons and glia isolated from different regions of the mouse brain. The magnitude of such increments was regionally specific for brain and also cell specific for such given regions.

The cholinergic effects of nicotine, although well-known, were further investigated on a subcellular level to specifically examine changes in the size of various cholinergic pools in the cerebral cortex. These results have indicated that administration of nicotine leads to a decrease in the acetylcholine content of both bound and vesicular storage pools without any alteration in the concentration of free acetylcholine.

The effects of nicotine were also examined in relation to the differential effect of this compound among environmentally conferred differences in learning ability. These previously published data have indicated that task-specific facilitative effects of nicotine exert different effects both behaviorally and metabolically depending upon the endogenous behavioral and metabolic baseline upon which they are superimposed. Such a model has been derived utilizing differentially housed mice. In animals treated with radioactive nicotine it was found that isolated animals showed a greater brain uptake, for several regions of nicotine, as compared to group housed mice, where the only appreciable uptake occurred in the basal ganglia; the latter change, however, was markedly below the uptake of nicotine shown by isolated animals. Nicotine metabolites, specifically cotinine, were also found

to be present in considerably greater quantities in several regions of the brain of isolated animals. This finding would be consistent with our previous suggestion that the facilitative effect of nicotine treatment upon the learning ability of behaviorally retarded mice (as result from early isolation housing) may be dependent upon a biologically active metabolite of nicotine, rather than to nicotine per se. A likely candidate for such a metabolite is cotinine, which we have observed to exert potent biochemical and behavioral effects in earlier studies.

In several studies we have also examined the regional differences in cerebral protein synthesis exerted by nicotine at several subcellular sites. In this regard, we have conclusively established that microsomal protein synthesis in mouse cerebral cortex is significantly augmented as a consequence of nicotine treatment, and further that the protein synthesis inhibition which may be environmentally produced by the stress of isolation housing may be completely reversed at the microsomal level by treatment with nicotine. In this respect preliminary studies of mitochondrial proteins from mouse cerebral cortex have indicated temporal qualitative and quantitative differences in the effects of nicotine. It is our purpose to further examine these changes and characterize them with respect to some of the metabolites of this compound.

In a final series of studies, the progress of which may be indicated at this point, it was shown that an experimentally-induced retrograde amnesia effected in mice with electroconvulsive shock could be antagonized or potentiated depending upon the interval of time between nicotine treatment and the post-conditioning amnesic event. In this

regard, it was shown that conditioned response retention was reduced below control levels if nicotine treatment was given 15 minutes prior to ECS, whereas if such treatment was effected 45 minutes prior to treatment approximately 80% of the animals showed antagonism toward the amnesic effect. These results again are consistent with our earlier findings and provide further support for the general working hypothesis that the role of nicotine in memory consolidation is to provide temporally related facilitative effects as are dependent upon aminergic and protein synthetic interactions in the central nervous system.

Publications Resulting from This Project

1. Essman, W.B. & Essman, S.G. Biphasic effects of nicotine upon ECS-induced retrograde amnesia in mice. Psych. Rep., 1973 (In Press).

2. Essman, W.B. Neuromolecular modulation of experimentally-induced retrograde amnesia. Confinia Neurol., 1973 (In Press).

3. Essman, W.B. Nicotine-related neurochemical changes: some implications for motivational mechanisms and differences. In: Dunn, W.J., Jr. (Ed.) Motivation in Cigarette Smoking, 1972 (In Press).